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09/426,776	10/26/1999	JEAK LING DING	1781-178P	2336

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BIRCH STEWART KOLASCH & BIRCH
PO BOX 747
FALLS CHURCH, VA 22040-0747

EXAMINER
HINES, JANA A

ART UNIT	PAPER NUMBER
1645	22

DATE MAILED: 05/06/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/426,776	DING ET AL.	
	Examiner	Art Unit	
	Ja-Na A Hines	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 February 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *30-54* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 February 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Amendment Entry

1. The amendment February 5, 2003 has been entered. Claims 1-9, 11-13, 15-17 and 26-29 have been cancelled. Claims 30-54 have been newly added. Claims 30-54 are under consideration in this office action.

Drawings

2. The corrected or substitute drawings were received on February 5, 2003. These drawings are acceptable.

Priority

3. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119.The benefit of the earlier filing date under 35 U.S.C. 119 has been denied for claims of the instant application. Applicant has not complied with the requirements of 37 CFR 1.63(c), since the oath, declaration or application data sheet does not acknowledge the filing of any foreign application. A new oath, declaration or application data sheet is required in the body of which the present application should be identified by application number and filing date. Applicants letter of October 1, 2002 indicates a claim for foreign priority filed on October 22, 1999 is not sufficient. No such claim for foreign priority is present in the record. Furthermore, the oath/declaration does not reflect any claim for foreign priority as asserted by applicants. Should applicants claim foreign priority then the oath/declaration is defective in not reciting the priority claim. It is further noted that a claim for a benefit of filing a provisional application under 119(e) is not a claim for foreign priority under 119(a)-(d).

Withdrawal of Rejections

4. The following rejection have been withdrawn in view of applicants amendments:

a) the rejection of claims 1-6 and 15-17 under 35 U.S.C. 112, first paragraph;

b) the rejection of claim 17 under 35 U.S.C. 112, second paragraph;

c) the rejection of claim 1 under 35 U.S.C. 102(b) as being anticipated by LaFleur et al. or Lim et al.

d) the rejection of claims 3-4 under 35 U.S.C. 103(a) as being unpatentable over Lim et al., as applied to claim 1 above, and further in view of Lee et al.; and

e) the rejection of claims 15-17 under 35 U.S.C. 103(a) as being unpatentable over Lim et al., as applied to claim 1 above, and further in view of Yarranton;

New Grounds For Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 30-54 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to an isolated nucleic acid comprising a nucleotide sequence encoding a secretory signal sequence comprising the amino acid sequence SEQ ID NO:10 or variants that comprise conservative replacement thereof that retain the biological activities of directing secretion of a fusion protein from a cell and cleavage of the secretory signal sequence from the fusion protein wherein the variations in said variants (a) relate to the G and D residues constituting the cleavage site and in said variations G and/or D are retained or D is replaced by E and /or G is replaced by A or V, (b) constitute at most 4 additions or deletions of amino acids in the secretory sequence, (c) result in the stretch of hydrophobic amino acids in the interior of the secretory sequence being 10-15 amino aids long and/or (d) constitute the overall substitution of fewer than 7 amino acids in the secretory sequence.

The specification and claims lack sufficient written description of the variant with all the claimed properties, (a) relate to the G and D residues constituting the cleavage site and in said variations G and/or D are retained or D is replaced by E and /or G is replaced by A or V, (b) constitute at most 4 additions or deletions of amino acids in the secretory sequence, (c) result in the stretch of hydrophobic amino acids in the interior of the secretory sequence being 10-15 amino aids long and (d) constitute the overall substitution of fewer than 7 amino acids in the secretory sequence.

There is no teaching of SEQ ID NO:10 or any amino acid sequence that comprises (a) relate to the G and D residues constituting the cleavage site and in said variations G and/or D are retained or D is replaced by E and /or G is replaced by A or V, (b) constitute at most 4 additions or deletions of amino acids in the secretory sequence, (c)

result in the stretch of hydrophobic amino acids in the interior of the secretory sequence being 10-15 amino aids long and (d) constitute the overall substitution of fewer than 7 amino acids in the secretory sequence and retains its biological activity.

The specification does not provide evidence that the claimed variant functions. The specification at page 23 described generic methods for amino acid substitution without specific reference to SEQ ID NO:10. In view of the lack of evidence, it is apparent that Applicants were not in possession of variants, at the time of filing the instant application. With the exception of the amino acid identified in SEQ ID NO:10, the skilled artisan cannot envision the detailed structure of the amino acid, thus conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. An adequate description requires more than a mere statement that it is part of the invention. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016. Thus an adequate description requires more than a mere statement that it is part of the invention, but rather the clearly defined portion itself is required.

See also, *In The Reagents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), where the court held that a generic statement that defines a genus of nucleic acids by only their functional activity does not provide an adequate description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide

sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

Thus, in the absence of sequence information of the variant amino acid sequence claimed the written description requirements fail. Therefore only the sequence set forth in SEQ ID NO:10, and not the full breadth of the claims meets the written description provision of 35 USC 112, first paragraph.

6. Claims 30-54 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to an isolated nucleic acid comprising a nucleotide sequence encoding a secretory signal sequence comprising the amino acid sequence SEQ ID NO:10 or variants that comprise conservative replacement thereof that retain the biological activities of directing secretion of a fusion protein from a cell and cleavage of the secretory signal sequence from the fusion protein wherein the variations in said variants (a) relate to the G and D residues constituting the cleavage site and in said variations G and/or D are retained or D is replaced by E and /or G is replaced by A or V, (b) constitute at most 4 additions or deletions of amino acids in the secretory sequence, (c) result in the stretch of hydrophobic amino acids in the interior of the secretory

sequence being 10-15 amino aids long and/or (d) constitute the overall substitution of fewer than 7 amino acids in the secretory sequence.

The specification teaches generic methods for creating amino acid substitutions. There is no teaching within the specification of any other amino acid sequence or variants comprising the characteristics of (a), (b), (c) and (d). The specification fails to teach examples of such variants that meet the limitations of the claims. Therefore, the specification fails to enable an isolated nucleic acid comprising a nucleotide sequence encoding a secretory signal sequence comprising the amino acid sequence SEQ ID NO:10 or variants that comprise conservative replacement thereof that retain the biological activities of directing secretion of a fusion protein from a cell and cleavage of the secretory signal sequence from the fusion protein wherein the variations in said variants (a) relate to the G and D residues constituting the cleavage site and in said variations G and/or D are retained or D is replaced by E and /or G is replaced by A or V, (b) constitute at most 4 additions or deletions of amino acids in the secretory sequence, (c) result in the stretch of hydrophobic amino acids in the interior of the secretory sequence being 10-15 amino aids long and/or (d) constitute the overall substitution of fewer than 7 amino acids in the secretory sequence.

Moreover, it is noted that (a) encompasses non-conservative amino acid substitutions, thus it is unclear what substitutions are being encompassed by the claims. Therefore, the specification fails to enable to the recited variants. There is no evidence that 4 additions or deletions of the amino acids in the secretory sequence that already

comprise conservative substitutions will the necessary biological activities. Therefore, the specification fails to enable the isolated nucleic acids.

Applicants have provided no guidance to enable one of ordinary skill in the art how to make, without undue experimentation, other variants. Given the lack of guidance contained in the specification and the unpredictability for making variants, one of skill in the art could not make or use the broadly claimed invention without undue experimentation.

Furthermore, the specification fails to provide an enabling disclosure for the use of any variants that meet the limitations recited in the claims. Applicants' have provided no guidance to enable one of ordinary skill in the art as to how determine, without undue experimentation, other variants. Given the lack of guidance contained in the specification and the unpredictability for determining an acceptable nucleic acid, one skilled in the art could not make or use the broadly claimed invention without undue experimentation.

7. Claims 30-54 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Neither the specification nor originally presented claims provides support for a secretory signal sequence comprising variants that comprise conservative replacement

thereof that retain the biological activities of directing secretion of a fusion protein from a cell and cleavage of the secretory signal sequence from the fusion protein wherein the variations in said variants (a) relate to the G and D residues constituting the cleavage site and in said variations G and/or D are retained or D is replaced by E and /or G is replaced by A or V, (b) constitute at most 4 additions or deletions of amino acids in the secretory sequence, (c) result in the stretch of hydrophobic amino acids in the interior of the secretory sequence being 10-15 amino aids long and/or (d) constitute the overall substitution of fewer than 7 amino acids in the secretory sequence.

Applicant did not point to support in the specification for the recited features of the variations of the signal sequence of SEQ ID NO:10. There appears to be no teaching of variants of SEQ ID NO: 10 comprising (a) relate to the G and D residues constituting the cleavage site and in said variations G and/or D are retained or D is replaced by E and /or G is replaced by A or V, (b) constitute at most 4 additions or deletions of amino acids in the secretory sequence, (c) result in the stretch of hydrophobic amino acids in the interior of the secretory sequence being 10-15 amino aids long and (d) constitute the overall substitution of fewer than 7 amino acids in the secretory sequence. Applicant has pointed to page 23 of the specification and claims for support of the amendment, however the entire specification appears to fail to recite support for the newly added limitation. There is no discussion of SEQ ID NO:10 at the cited page. There is no discussion of a variant comprising all of the recited substitutions. There is no support in the specification. Therefore, applicants must specifically point to

page and line number support for the newly added amendments. Therefore, the new claims incorporate new matter and are accordingly rejected.

8. Claims 30-54 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 30 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 30 is vague and unclear. The claims recites the variations in said variants are defined in (a), (b), (c) and/or (d). It is unclear whether the variants comprise all of the characteristics of (a), (b), (c) and (d) or if the claims are in the alternative and only comprise variations in any one of (a), (b), (c) or (d). The meaning of the "and/or" makes the claims vague and unclear. Clarification is required to overcome the rejections. See also claims 37 and 49.

Claim 30 also recites that the amino acid sequences comprises conservative replacements thereof. It is unclear if the entire sequence can have conservative replacements or only specific amino acids. It is unclear how to distinguish which amino acids are being conservatively replaced thereof. The metes and bounds of the claim language are unclear.

Similarly, it is unclear how to define the "and/or" in subsection (a). Must all of the variations occur, or only either substituting the G or the D. It is unclear what alternatives must occur and what alternatives are optional. Clarification is required to overcome the

rejection. The metes and bounds of the claims cannot be ascertained; thus the claims are unclear.

Abbreviations like A, D,E, G and V must be spelled out when used for the first time in a chain of claims.

9. Claims 31 and 38 are drawn to at least 1 and up to 3 amino acid replacements, it is unclear how to define the "and/or" used in the claims. Must all 3 changes occur or only 1 or 2 substitutions. The metes and bounds of the claims are unclear.

10. The term "desired heterologous protein" in claims 37 and 41 is a relative term which renders the claim indefinite. The term "desired" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The metes and bounds of desired cannot be ascertained; what makes a protein desirable? It is unclear what characteristics make the protein undesirable. Thus, the metes and bounds of the claims are unclear. Claim 48 has the same issue.

11. Dependant claim 39 recites wherein said amino acid sequence is SEQ ID NO:10, However Claim 37 refers to the amino acid sequence SEQ ID NO:10 or variants of said amino acid sequence and a linking amino acid sequence. It is unclear which said amino acid sequence claim 39 is referring too. Claim 51 has the same issue. Clarification is required to overcome the rejection.

Conclusion

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is (703) 305-0487. The examiner can normally be reached on Monday through Thursday from 6:30am to 4:00pm. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Ja-Na Hines
May 1, 2003